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Published in:
Journal of comparative physiology a-Neuroethology sensory neural and behavioral physiology

DOI:
10.1007/BF00198350

J Comp Physiol A (1991) 168:305–312

Journal of Comparative Physiology A Sensory, Neural, and Behavioral Physiology

Receptor potential and light-induced mitochondrial activation in blowfly photoreceptor mutants

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Accepted December 28, 1990

Summary. 1. Simultaneous measurements of the receptor potential and the light-induced mitochondrial activation were performed in white-eyed blowflies *Calliphora vicina*, mutant *chalky*, and *Lucilia cuprina*, mutants w^F and *w'nss*. The intensity dependence and the temporal dynamics were investigated.

2. The characteristic curve of the light-induced mitochondrial activation vs. log intensity has an S-like shape, which is much steeper than the characteristic curve of the receptor potential (the V/log I curve). The threshold intensity of mitochondrial activation elicits about a half-maximal receptor potential, while mitochondrial activation and photoreceptor potential saturate at about the same intensity.

3. The time course of the mitochondrial activation induced by a light flash, i.e. the pulse-response curve, is biphasic in both mutants with normal phototransduction properties, *Calliphora chalky* and *Lucilia* w^F; the shape is slightly species dependent.

4. In the phototransduction mutant *Lucilia w'nss* the step-responses of both the (bright) light-induced mitochondrial activation and receptor potential are quite different from the corresponding signals in *Lucilia* w^F. The striking resemblance of the step-response of the mitochondrial activation to its pulse-response indicates that mitochondrial activation and receptor potential are intimately linked.

Key words: Blowfly – Photoreceptor – Receptor potential – Mitochondrial activation – Calcium

Introduction

The retina of blowflies is a metabolically highly active tissue. The oxygen consumption by the retina, which is already high in the dark, is strongly enhanced by illumination (e.g. Hamdorf et al. 1988). Most probably, the main reason is that light causes a decrease in the membrane resistance of the photoreceptor cells. The resulting current decreases ion gradients that have to be replenished by the energy-consuming sodium-potassium pump. The enhanced demand in energy due to illumination is met by the enhanced activity of the mitochondria in the photoreceptors. Presumably, both the light-induced rise in ATP turnover and the intracellular calcium concentration play a crucial role in the mitochondrial activation (Hamdorf et al. 1988; Tinbergen and Stavenga 1987).

The metabolism of blowfly photoreceptor cells can be studied in vivo in white-eyed mutants via fluorescence measurements (Stavenga and Tinbergen 1983). Changes in the blue-induced green fluorescence reflect changes in the redox state of the mitochondrial flavoproteins, thus indicating changes in the oxidative metabolism (Tinbergen and Stavenga 1986). The action spectrum of a criterion change in the blue-induced green fluorescence closely resembles the absorption spectrum of the visual pigment as well as the spectral sensitivity measured electrophysiologically, indicating that the fluorescence change is linked to the visual transduction pathway (Tinbergen and Stavenga 1987).

In this paper we analyse the relation between phototransduction and oxidative metabolism in more detail. We have determined the intensity dependence and the pulse-response of the light-induced mitochondrial activation, by measuring simultaneously the receptor potential and the blue-induced green fluorescence. Furthermore, we have analysed the mitochondrial activation in a phototransduction mutant that features an anomalous, transient receptor potential upon illumination with bright light.

Material and methods

Animals. White-eyed blowflies *Calliphora vicina* (mutant *chalky*) and *Lucilia cuprina* (mutants w^F and *w'nss;* kindly provided by Dr. G.G. Foster, CSIRO Canberra, Australia) were raised on liver and

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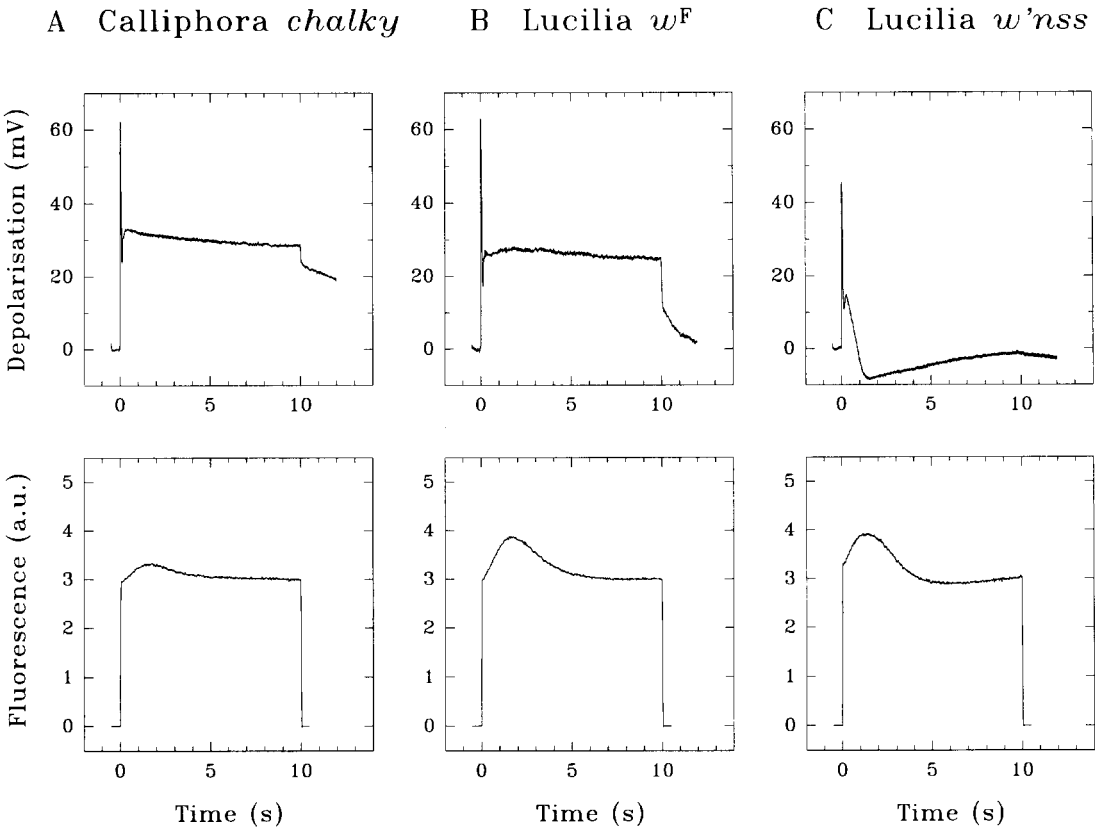

Fig. 1A–C. Simultaneous recordings (single traces) of receptor potential and blue-induced green fluorescence in *Calliphora chalky* (**A**), *Lucilia* w^F (**B**) and *Lucilia w'nss* (**C**); the stimulus consisted of 10 s blue light 477 nm, $\log_{10}(I/I_{max}) = 0$, after 120 s dark adaptation

fed with water, sugar, carrot juice and liver. These mutants are used here, because it is possible to measure the blue-induced green fluorescence in white-eyed flies only; their phototransduction properties appear equal to those of wild type flies. The *Lucilia* double mutant *w'nss* has in addition to the absence of screening pigment a mutation in the visual transduction chain; as in the *t*ransient *r*eceptor *p*otential mutant of *Drosophila melanogaster, trp,* the receptor potential of *Lucilia w'nss* has *n*o *s*teady *s*tate (see Fig. 1c; Howard 1984; Barash et al. 1988). This mutation is a recessive point mutation, located on the fourth chromosome (Howard 1984).

Preparation. Flies were taken 10 to 20 days after emergence. They were immobilised with wax, leaving the spiraculae and the abdomen free, and fed with honey diluted in water. Before each experiment the visual pigment concentration was checked with red-induced far-red fluorescence (Stavenga 1983).

Experimental setup. The fly was mounted on a Universal stage of a Leitz Orthoplan microspectrophotometer equipped with a Leitz NPL10 objective (aperture 0.20). A Peltier element maintained the temperature of the fly at approximately 16 °C. The stimulus light was delivered by a 75 W Xenon arc lamp, controlled by a fast shutter (Uniblitz, A.W. Vincent Associates, Inc, Rochester NY, USA). The stimulus intensity could be attenuated with neutral density filters (Schott DAL) and neutral density wedges (Smakman and Pijpker 1983). The setup is computer controlled via an intelligent laboratory interface (1401, Cambridge Electronic Design, Cambridge UK) using ASYST (Macmillan Software Company, New York USA).

Electrophysiology. Before mounting the fly, a small hole of approximately 50 facet lenses was cut in the cornea and covered with white soft paraffin. Through the hole a conventional glass microelectrode (filled with 3 *M* KAc/0.05 *M* KCl; 100–150 MΩ) and a glass micro-electrode with broken tip as reference electrode (filled with fly Ringer solution (in m*M*): 130 NaCl, 2 KCl, 2 $CaCl_2$, 5 $MgCl_2$ and 10 Hepes pH 7.0) were introduced. Intracellular recordings were made from the photoreceptor cells R1–6 (Hardie 1979). The membrane potential was recorded with a home built electrophysiology amplifier (Muijser 1979a). The signal was electronically amplified and low-pass-filtered (Tektronix AM502; −3 dB point at 300 Hz) and sampled at 1 kHz by the CED1401 interface. Before each stimulus the visual pigment was reset to 100% xanthopsin with 5 s red light (600 nm; $2.4 * 10^{15}$ quanta · cm^{-2} · s^{-1}; see e.g. Hamdorf 1979) and the fly was dark-adapted for 2 min.

Fluorometry. For measuring the mitochondrial activation, epifluorescence was excited by a blue light beam (477 nm interference filter from Schott DAL; intensity $2.3 * 10^{15}$ quanta · cm^{-2} · s^{-1}). The emission was spectrally filtered in the green with a Balzers K55 (peak 550 nm) and measured with a Hamamatsu R928 photomultiplier. This signal was electronically low-pass-filtered (cutoff frequency 15 Hz) and sampled at 100 Hz by the CED1401 interface.

Results

Light-induced mitochondrial activation

Illumination of the dark-adapted eye of a blowfly lacking screening pigments with an intense blue light yields a receptor potential and a green fluorescence (Fig. 1). The receptor potential of an individual photoreceptor cell and the green fluorescence of several hundreds of photoreceptor cells were measured simultaneously. The

receptor potential shows the characteristic depolarization with a rapid initial peak followed by a plateau that is reached within 150 ms (e.g. Laughlin 1981; Barash et al. 1988). The fluorescence shows a biphasic response with a maximum after 1–2 s; the plateau is reached in about 5 s (see Stavenga and Tinbergen 1983).

The receptor potentials and mitochondrial responses of the mutants *Calliphora chalky* and *Lucilia* w^F are very similar (Fig. 1A and 1B), although the transient change in fluorescence is usually more pronounced in *Lucilia* than in *Calliphora*.

In the phototransduction mutant *Lucilia w'nss*, however, the receptor potential decays rapidly (Fig. 1C), to reach the resting membrane potential within 1 s (Howard 1984; Barash et al. 1988). The green fluorescence in *Lucilia w'nss* has a maximum after 1–2 s, like in the mutants with normal phototransduction properties, but the maximum is followed by a trough at 5–8 s and a subsequent increase. Clearly, in the phototransduction mutant *w'nss* both the receptor potential and the mitochondrial activation deviate from the corresponding signals in the mutants where phototransduction is normal.

Light intensity dependence of mitochondrial activation

The simultaneous measurement of receptor potential and fluorescence allows a quantification of the intensity dependence of both phototransduction and mitochondrial activation in one and the same preparation and in vivo. A disadvantage of the fluorescence method, however, is that intense blue light is necessary; low intensities do not excite a measurable fluorescence. As a consequence, the test illumination is a stimulus in itself. Nevertheless, we are able to determine the intensity dependence of the mitochondrial activation by using the approach of Fig. 2, where the mitochondrial activation elicited by a flash of variable intensity is tested by a subsequent bright blue illumination (see also Tinbergen and Stavenga 1987).

In Fig. 2A an initial 0.2 s stimulus (Fig. 2C) of white light causes a pronounced depolarization of the receptor potential. After a time delay of 0.5 s darkness, the fly is illuminated with bright blue light (Fig. 2C) that causes a second pronounced depolarization of the receptor potential (Fig. 2A). Furthermore, the blue illumination excites a green fluorescence (Fig. 2B). Without the preceding white light, the blue illumination induces a fluorescence with a much lower initial value (dashed line in Fig. 2B). The white flash clearly induces mitochondrial activation as expressed by the higher initial fluorescence, monitored by the subsequent blue illumination. The difference in initial fluorescence therefore can be used as a measure for the mitochondrial activation.

Figure 3 presents the receptor potential induced by 0.2 s stimuli of white light of different intensities (left panels in Fig. 3A–C), together with the change in fluorescence induced by the subsequent blue light (continuous curves in right panels in Fig. 3A–C). At the higher intensities the depolarization shows a peak-to-plateau transition (see e.g. Laughlin 1981). At these higher intensities the subsequent fluorescence starts to deviate from that measured after the low intensity flashes in all three mutants, i.e. in both white-eyed blowfly mutants *Calliphora chalky* and *Lucilia* w^F with normal phototransduction properties as well as in the phototransduction mutant *Lucilia w'nss*. The deviations are immediately apparent by comparing the responses with the fluorescence induced in a dark-adapted eye (dashed curves in right panels in Fig. 3A–C).

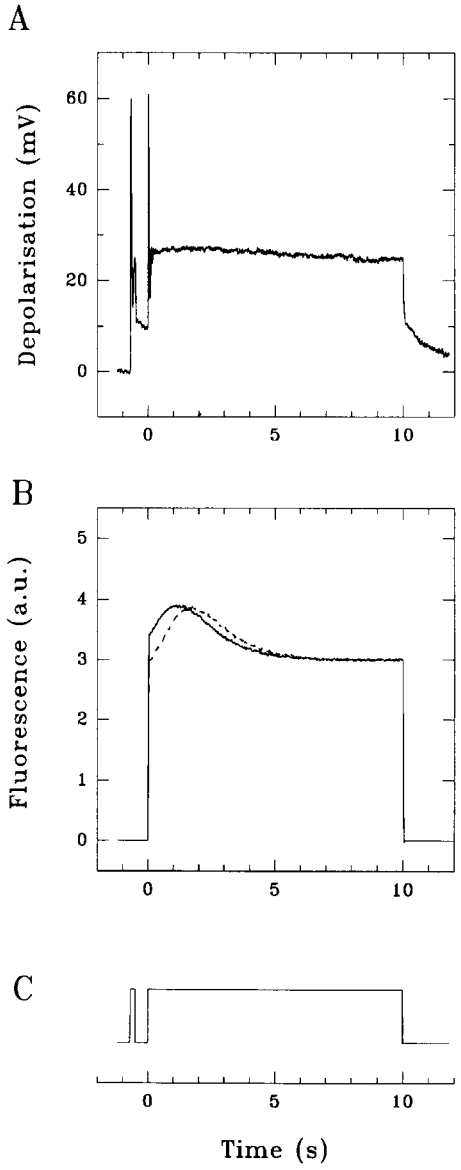

Fig. 2A–C. Method used to obtain intensity dependence of mitochondrial activation shown in Fig. 4; **A:** receptor potential; **B:** blue-induced green fluorescence; **C:** test sequence consisting of 120 s dark-adaptation, a 0.2 s white stimulus followed by a 0.5 s fixed time delay and a 10 s flavoprotein fluorescence test (477 nm). In **B** drawn line: fluorescence induced by 10 s test light after stimulus $\log_{10}(I/I_{max}) = -1.6$; dotted line: fluorescence without preceding stimulus

The experimental data of Fig. 3 have been used to construct the intensity/response functions of Fig. 4. The receptor peak potential (V_{peak}) was determined by taking the average of a 5 ms interval symmetrically around the

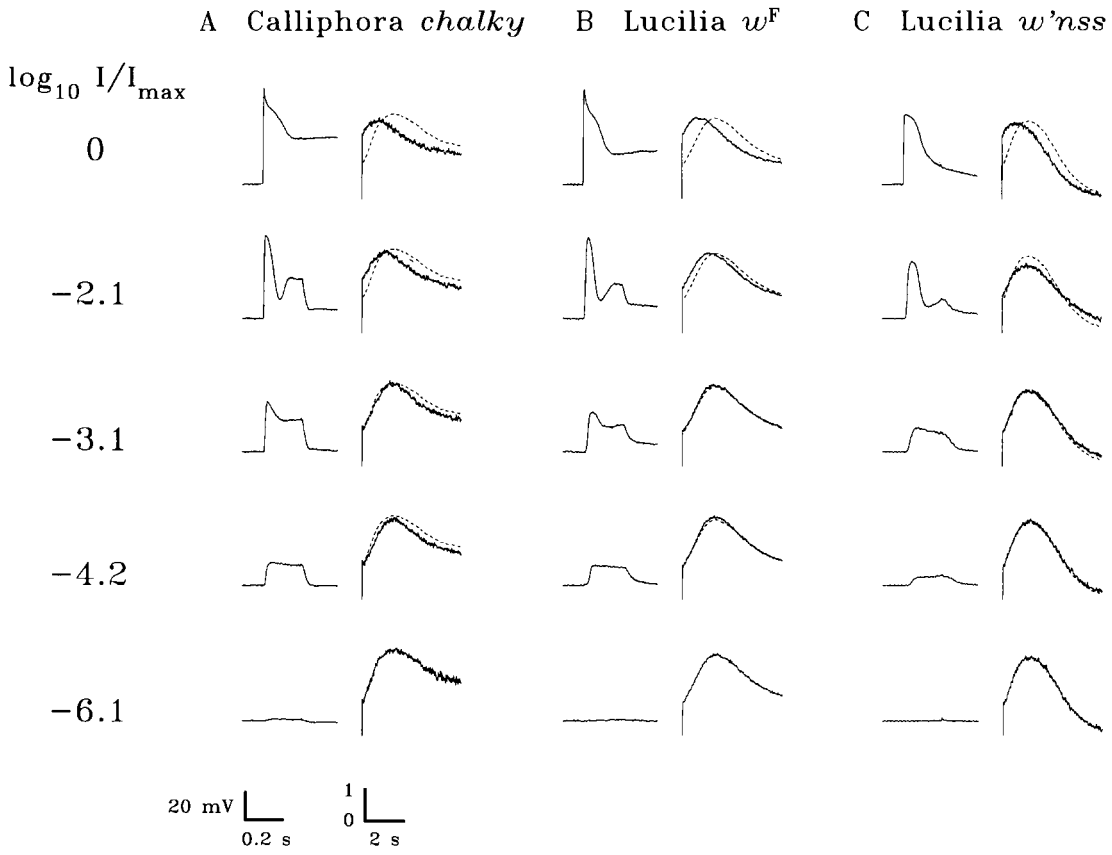

Fig. 3A–C. Effect of 0.2 s stimulus of white light on receptor potential and blue-induced green fluorescence using stimulus regime presented in Fig. 2; stimulus intensities used are indicated as $\log_{10}(I/I_{max})$; **A:** *Calliphora chalky*; **B:** *Lucilia* w^F; **C:** *Lucilia w'nss*; traces are average of 4 sweeps; **A–C** left panels: full receptor potential; **A–C** right panels: transient part of fluorescence (scale bar 0–1 indicates difference in initial fluorescence of response to $\log_{10}(I/I_{max}) = -6.1$ and 0, respectively); in order to facilitate comparison between the fluorescence signals, the response to $\log(I/I_{max}) = -6.1$ is included as dashed trace

maximum of the receptor potential depolarization, and the receptor plateau potential ($V_{plateau}$) by taking the average of the last 25 ms of the plateau phase. Furthermore, the mitochondrial activation was estimated by taking the difference between the averages of the initial 100 ms and the last 0.5 s of the fluorescence signal, and presented in Fig. 4 after normalization.

The intensity/response functions of the receptor potential in all three blowfly mutants have a similar shape and range. Also, the intensity/response functions of the mitochondrial activation resemble each other, but the intensity range is much narrower than that of the receptor potential. The threshold intensity of the mitochondrial activation induces approximately a half-maximal peak potential and the light-induced mitochondrial activation saturates when the photoreceptor saturates.

Comparing the two *Lucilia* mutants, w^F and *w'nss*, shows that the intensity dependence of the mitochondrial activation is very similar. The $V/\log I$ curve of the plateau potentials of *Lucilia w'nss* shows at higher stimulus intensities no pronounced decay to the resting membrane potential, because the 0.2 s duration of the stimulus is too short to cause the *nss*-effect, even at the highest intensity applied (cp. the 10 s stimulus duration in Fig. 1C). A marked difference exists between the peak potentials. In *w'nss* the maximum peak potential is 45–50 mV, characteristically lower than the 60–65 mV in *Lucilia* w^F (or *Calliphora chalky*).

The pulse-response of mitochondrial activation

The step-response of the mitochondrial activation in the phototransduction mutant *Lucilia w'nss* differs distinctly from the one in *Lucilia* w^F. Since *Lucilia w'nss* has only a transient receptor potential, we hypothesized that the anomalous step-response of *Lucilia w'nss* might be related to the short-living receptor potential. Therefore we analysed the time course of mitochondrial activation in *Lucilia* w^F, i.e. the mutant with normal phototransduction, after a short flash.

A 0.2 s stimulus of white light was applied and the blue-induced green fluorescence was measured at different times after the stimulus (see Fig. 5). Individual fluorescence traces, each resulting from a test illumination after a specific time interval, are superimposed in Fig. 5A. The first 100 ms of the fluorescence were averaged and this was taken to represent the response value. We will call the dashed line, drawn through the averages, the pulse-response of the mitochondrial activa-

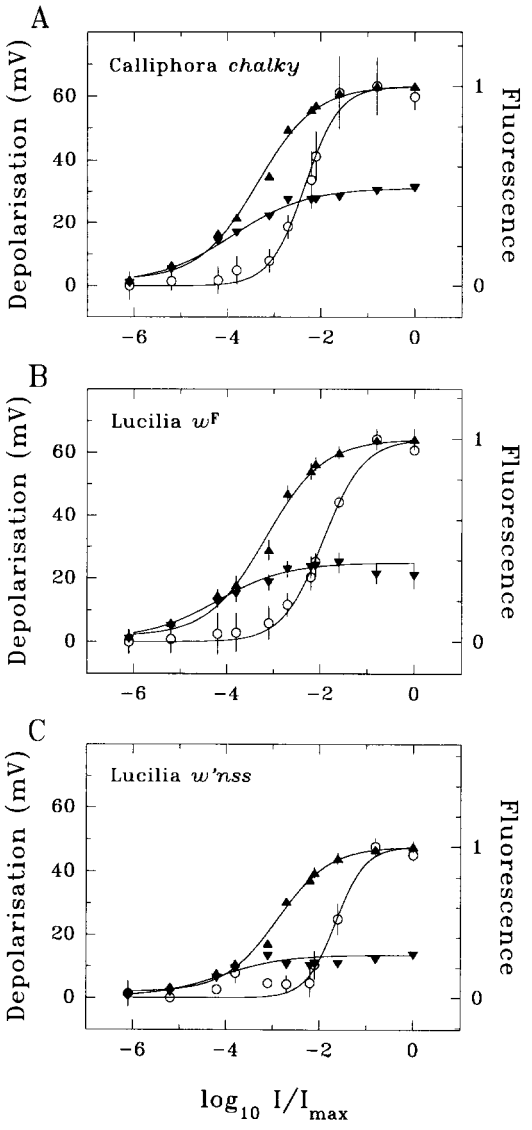

Fig. 4A–C. Intensity/response functions of V_{peak} (–▲–), $V_{plateau}$ (–▼–) and mitochondrial activation (–○–) in *Calliphora chalky* (**A**), *Lucilia* w^F (**B**) and *w'nss* (**C**); data points average of 4 sweeps, error bars represent standard deviation. The hyperbolic function

$$f(I) = \frac{(R \cdot I)^n}{(R \cdot I)^n + 1}$$

was fitted to the data of V_{peak}, $V_{plateau}$ and mitochondrial activation (see Matič and Laughlin 1981; Laughlin 1981) with an iterative algorithm using the Gauss–Newton method available in ASYST

tion. The pulse-responses for 5 different stimulus intensities, shown in Fig. 6, follow a biphasic time course with a peak after 1–2 s and a trough at about 10 s.

The pulse-responses of *Calliphora* and *Lucilia* show 2 small differences (Fig. 6A and 6B). Firstly, the trough at about 10 s is much more pronounced in *Lucilia* that in *Calliphora*. Secondly, in *Calliphora* virtually only the amplitude of the pulse-response varies with intensity, while in *Lucilia* the pulse-response also becomes distinctly faster with increasing intensity. These differences reflect small but clear differences between the species in the mechanism of mitochondrial activation.

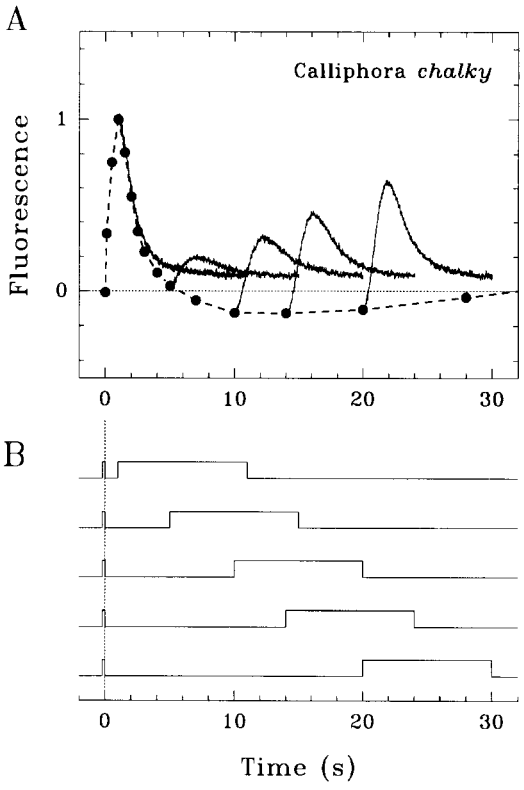

Fig. 5A, B. Method used to obtain pulse-responses of Fig. 6. **A:** drawn lines: superimposed individual traces of the blue-induced green fluorescence (only transient part is shown); dashed line connects averages of initial 100 ms of fluorescence traces and represents pulse-response. **B:** graphical representation of stimulus regime used; for each time delay a 0.2 s white stimulus was followed at the appropriate time by a blue test illumination; shown are $t_d = 1$ s, 5 s, 10 s, 14 s and 20 s

Discussion

The intensity dependence of the mitochondrial activation

To investigate the intensity dependence of the light-induced mitochondrial activation, we have measured simultaneously the receptor potential and the blue-induced green fluorescence (e.g. Fig. 1). The receptor potentials were recorded intracellularly in individual R1–6 photoreceptor cells. The fluorescence signal, reflecting mitochondrial activation, stems from several hundreds of photoreceptor cells of the same class (Tinbergen and Stavenga 1987). We have concluded that the two signals reveal two aspects of phototransduction in R1–6 photoreceptor cells.

The intensity dependence of the light-induced mitochondrial activation (Fig. 4) was established by measuring the effect of a 0.2 s light stimulus on the flavoprotein redox state 0.5 s later. We chose this time interval because stimuli of increasing intensity cause a monotonic increase of the initial fluorescence during the first second of illumination (see Fig. 6). The present experiments show that the intensity dependence of the mitochondrial activation is closely correlated to the intensity dependence of the receptor potential. Clearly, mitochondrial

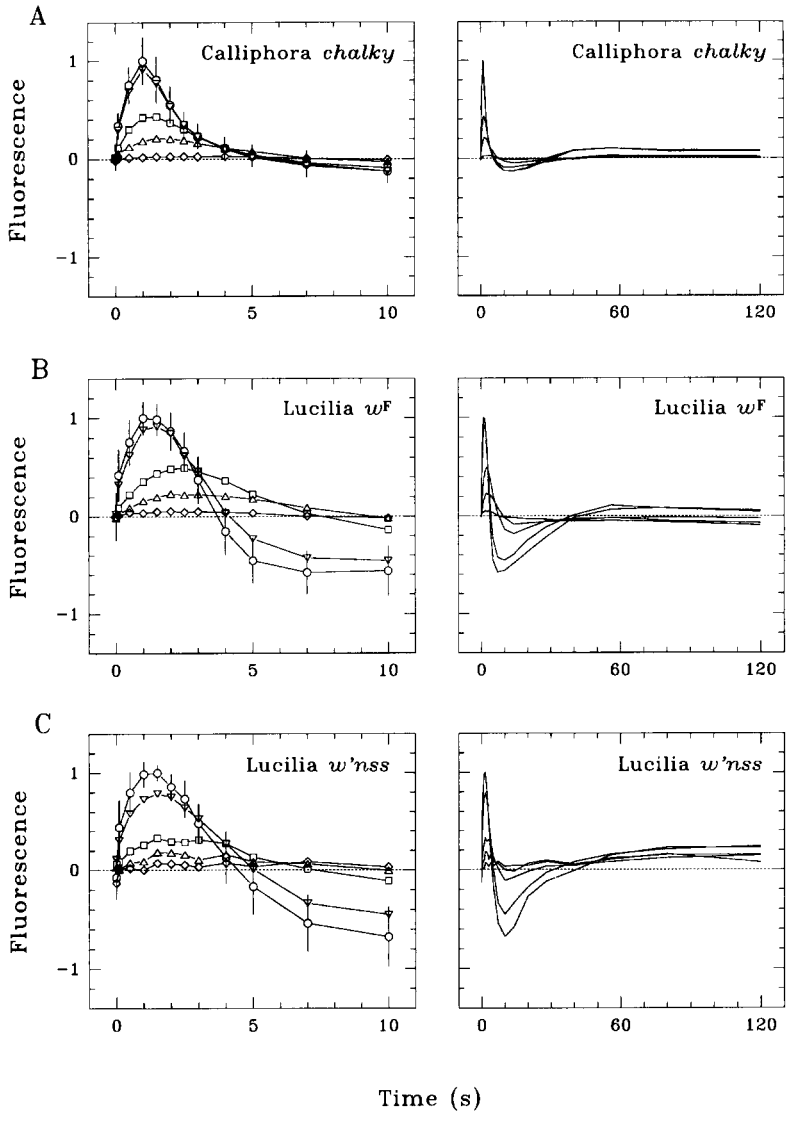

Fig. 6A–C. Pulse-response curves of mitochondrial activation in *Calliphora chalky* (**A**) *Lucilia* w^F (**B**) and *w'nss* (**C**); time between 0.2 s stimulus and test illumination varied from 0 to 120 s (left panels show 0–10 s; right panels 0–120 s); –○–, –▽–, –□–, –△–, –◇–, respectively $\log_{10}(I/I_{max}) = 0$, −0.8, −2.1, −3.1 and −4.2; data points average of at least 4 sweeps, error bars represent standard deviation

activity, i.e. ATP production, constitutes an important part of the phototransduction process (Hamdorf et al. 1988). The link between mitochondrial activation and phototransduction is not yet clarified, however.

Tinbergen and Stavenga (1987) have discussed that a light-induced increase of the intracellular calcium concentration $[Ca^{2+}]_i$ is a likely cause for the mitochondrial activation. Our results corroborate this suggestion. The dynamic range of the mitochondrial activation coincides with two processes that are known to be dependent on the $[Ca^{2+}]_i$, namely the peak-to-plateau transition of the receptor potential and the pupil response. The intensity threshold of the mitochondrial activation is at about the intensity where the receptor potential starts to show a peak-to-plateau transition. This transition is a $[Ca^{2+}]_i$ dependent process (e.g. Muijser 1979b).

Wild type *Calliphora* and *Lucilia* possess a so-called longitudinal pupil. Their photoreceptors contain pigment granula that are moving towards the rhabdomere when the flies are illuminated with high intensities, thereby reducing the light flux. The intensity dependence of the pupil response in the distal part of the photoreceptor of *Calliphora vicina* was established by Roebroek and Stavenga (1990) in relation to the $V/\log I$ curve of the receptor potential (see also Howard et al. 1987). Interestingly, the threshold for the pupil response is at about the intensity where the peak potential is half-maximal, alike that for the mitochondrial activation. The pupil response is under direct control of visual pigment activation (Bernard and Stavenga 1979), via $[Ca^{2+}]_i$ (Kirschfeld and Vogt 1980; Howard 1984).

To summarize, the correspondence in the intensity dependences suggests that the mitochondrial activation is mediated by an increase of $[Ca^{2+}]_i$. Bygrave et al. (1975) have shown that mitochondrial respiration in the flight muscle of the blowfly *Lucilia cuprina* can be stimulated by an increase of $[Ca^{2+}]_i$. In tissues of all vertebrate sources studied so far, a role for $[Ca^{2+}]_i$ in the regulation of mitochondrial activity has been shown (e.g. from rats: heart, skeletal muscle, kidney, liver, brain, white and brown adipose tissue and mammary tissue; from trout, pigeons, frogs and humans: heart tissue;

McCormack et al. 1990). In these tissues calcium stimulates the activity of 3 mitochondrial dehydrogenases (McCormack et al. 1990). Also the activity of the H^+–ATP synthase complex depends on $[Ca^{2+}]_i$ (Yamada et al. 1980).

In blowflies possibly the dominant cause for a light-induced increase in $[Ca^{2+}]_i$ is the influx of extracellular calcium (Sandler and Kirschfeld 1986). Removing the extracellular calcium thus would prevent this calcium influx. We have preliminary evidence showing that lowering the extracellular calcium concentration to approximately 1 n*M* indeed eliminates mitochondrial activation.

Mitochondrial activation in the phototransduction mutant Lucilia w'nss

The intensity dependence of the light-induced mitochondrial activation in the *Lucilia* mutants w^F and *w'nss* is similar (Fig. 4B and 4C). Also, the pulse-response of the mitochondrial activation in *Lucilia* w^F and *Lucilia w'nss* are virtually identical (Fig. 6B and C). However, the step-responses deviate after approximately 3 s (compare Fig. 1B to 1C); the step-response of the mitochondrial activation in *Lucilia w'nss* resembles its pulse-response.

We recall that the receptor potential of the phototransduction mutant *Lucilia w'nss* has *n*o *s*teady *s*tate (Fig. 1C; Howard 1984; Barash et al. 1988). At high intensities, the plateau phase of the receptor potential decays within one second to the resting membrane potential and the photoreceptor becomes insensitive to light. Furthermore, the amplitude of the receptor potential in *Lucilia w'nss* is distinctly smaller than that in *Lucilia* w^F (Fig. 4B, C). The dynamics of the receptor potential in *Lucilia w'nss* are also different. We found that the receptor potential consistently has a longer response latency at all light intensities, while the decay to baseline occurs at bright illuminations only (data not shown; but see Barash et al. 1988).

These phenomena are not a severe form of light adaptation, but stem from a reduced excitation efficiency (Barash et al. 1988). As a result, the phototransduction process is only transiently activated. Presumably, the pulse-response-like behaviour of the mitochondrial fluorescence in *Lucilia w'nss* during prolonged blue illumination reflects a transient mitochondrial activation that is related to the shut-down of the phototransduction mechanism.

Both a decay to baseline and a reduced amplitude and increased response latency can be induced by applying lanthanum ions extracellularly to photoreceptors of *Calliphora chalky,* as discovered by Hochstrate (1989). Although lanthanum is known to affect the intracellular calcium concentration, Hochstrate (1989) concluded that the La^{3+} effects are not primarily caused by changes in the calcium metabolism. However, calcium acts in photoreceptor cells at several stages, at least in both excitation and adaptation (Fein and Payne 1989). We therefore suspect that, due to the *nss* defect, a modified calcium metabolism does play a crucial role in the phototransduction mutant. We conclude that phototransduction and mitochondrial activation are intimately linked. Measuring mitochondrial activation via fluorescence offers an attractive, alternative means for studying the phototransduction process in fly photoreceptors.

Acknowledgements. This research was supported by the Netherlands Organization for Scientific Research (NWO) through the Foundation of Biophysics (Stichting voor Biofysica).

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